Vulnerability of memory function and the hippocampus

Klaming Miller, R.

2019

CHAPTER 7

GENERAL DISCUSSION

The hippocampus is particularly vulnerable to injury and degeneration. The most prominent symptom of damage to this brain region is impaired memory function. The exact function of the hippocampus is however still a matter of debate. Traditionally, the hippocampus has been viewed as a structure mainly involved in the formation and retrieval of episodic and semantic long-term memories and spatial memories. More recently, the anatomy of the hippocampus has been subdivided into functional compartments: the posterior hippocampus performing cognitive functions, while the anterior hippocampus is involved in the regulation of stress and emotions as well as the response to threat and fear (Bartsch & Wulff, 2015; Fanselow & Dong, 2010). Accordingly, the hippocampus has been implicated in affective and stress-related psychiatric disorders, such as posttraumatic stress disorder (PTSD; Mayo & Heilig, 2018) and depression (Liu et al., 2017), and is the target of pharmacological interventions for these conditions (Boldrini et al., 2009; Vermetten, Vythilingam, Southwick, Charney, & Bremner, 2003). It is firmly established that the hippocampus is a key brain region for the formation of declarative memories, including episodic, semantic, autobiographical, and spatial information (Broadbent, Squire, & Clark, 2004; Cabeza & Jacques, 2007; Eichenbaum, 2001; Zola-Morgan & Squire, 1993). Nevertheless, there is still diverging evidence in the field regarding the functional and structural correlates of the hippocampus in cognitive and affective disorders.

The aim of this dissertation was to investigate three separate conditions that selectively target the hippocampus and its function. Specifically, we conducted neuropsychological and neuroimaging studies to better understand the effects of lifestyle and personality, PTSD, and Herpes Simplex Encephalitis on the memory system. The focus was on investigating which factors slow down or accelerate decline in memory function as well as the functional and structural consequences of psychological trauma and disease on the hippocampus. Data used to answer these research questions was gathered from three sources, i.e. the Longitudinal Aging Study Amsterdam (LASA), a cohort of combat-exposed veterans with and without PTSD (VA San Diego), and a unique case study (patient A.V.). In addition, we conducted a meta-analysis of voxel-based morphometry (VBM) studies measuring the overlap of gray matter volume loss in PTSD and alcohol use disorder. The following sections provide a summary of the results discussed within the framework of methodological limitations and recent findings in the field. Conclusions are drawn with regards to clinical implications and directions for future research.

DISCUSSION

The present work highlights that the hippocampus is a brain structure that is susceptible to injury, disease, and degeneration of diverse etiologies, spanning from age-related changes to various neuropsychiatric disorders. There are a number of neurobiological characteristics of the hippocampus that are important to consider when discussing present study findings. For example, the hippocampus is one of few brain regions that have the potential to produce new neurons, a process called neurogenesis (Bartsch &

Wulff, 2015; Kempermann et al., 2018; Lie, Song, Colamarino, Ming, & Gage, 2004). Neurogenesis likely contributes to learning and memory performance, and can be stimulated by environmental and lifestyle factors. Impaired hippocampal neurogenesis, on the other hand, can lead to compromised memory performance and abnormal emotion regulation (Bettio, Rajendran, & Gil-Mohapel, 2017). The hippocampus is also known for its neuroplasticity (Mayo & Heilig, 2018). Neuroplasticity can occur on several different levels, including changes in the synapses, dendrites, and axons, leading to reorganization or strengthening of neural networks (Bartsch & Wulff, 2015). Such changes can be triggered by intrinsic or extrinsic stimuli in response to disease or injury as well as by therapeutic interventions or the environment, and can lead to adaptive or maladaptive behavioral changes (Cramer et al., 2011).

The aim of **chapter 2** was to understand to what degree lifestyle factors account for individual differences in age-related decline of episodic memory function. Modifiable lifestyle factors that were examined included physical activity, smoking tobacco, sleep habits, alcohol consumption, and social engagement. While the role of these factors in memory decline has been the focus of previous research, results have been inconsistent so far. Methodological strengths of this study include a longitudinal research design (14 year period) with a large cohort (N=1,966), comprehensive neuropsychological assessment, as well as controlling for comorbidities (i.e., depression, chronic diseases, and functional limitations) and possible confounding factors (i.e., verbal intelligence and demographic variables such as gender and socioeconomic status). Findings from this study were mostly in line with our hypotheses. Results showed that physical activity, light/moderate alcohol consumption and social engagement were associated with better memory function, while smoking tobacco and excessive sleep were associated with worse memory function. There were no associations between the rate of memory decline and lifestyle factors, except for sleep duration.

The beneficial effects of physical activity and light/moderate alcohol consumption and the negative effects of smoking on the cardiovascular system, and thus brain health, likely explain these findings. Physical activity has been linked to neurogenesis and increased synaptic plasticity (Cotman, Berchtold, & Christie, 2007) as well as to hippocampal volume (Erickson, Hillman, & Kramer, 2015). Light to moderate alcohol consumption has been associated with reduced risks of stroke and congestive heart failure (O'Keefe, Bhatti, Bajwa, DiNicolantonio, & Lavie, 2014). Smoking tobacco, on the other hand, causes inflammation and oxidative stress (Bruno & Traber, 2006) as well as decreased gray and white matter densities (Meyer et al., 1999). The mechanisms behind the beneficial effects of social interactions on memory function may be that staying actively involved in the community acts as a type of "cognitive brain training". Studies have consistently shown a positive relation between social activity and cognitive function (Bennett, Schneider, Tang, Arnold, & Wilson, 2006; Cacioppo & Hawkley, 2009; Krueger et al., 2009). In addition, being socially engaged may indirectly motivate older adults to take care of their health and provide a sense of purpose.

Based on our findings of the significant effects of lifestyle factors on memory function in older adults, we followed up on the cohort by assessing the role of personality traits on age-related memory decline (Chapter 3). We selected personality traits that determine how individuals respond to stress and life challenges as well as their likelihood to engage in certain behaviors that are linked to brain health, such as those discussed in Chapter 2. A total of 1,966 men and women aged 65 years and older rated their own personality and participated in comprehensive memory assessments every three years for 14 years. We found that higher levels of mastery and self-efficacy were associated with better memory function. High neuroticism, on the other hand, was linked to worse memory function. The rate of decline was not affected by personality traits, suggesting that the examined personality traits are not directly linked to dementia or abnormal cognitive aging.

There are a number of mechanisms that likely account for the effects of personality on memory function. Individuals with low self-efficacy or mastery may feel less equipped to deal with challenges, and may consequently avoid socially and mentally stimulating activities. Such lack of engagement may lead to cognitive decline according to the "use it or lose it" theory (Bandura, 1989; Seeman, McAvay, Merrill, Albert, & Rodin, 1996). In addition, older adults with a higher sense of personal control may be more likely to live independently and may be better equipped to successfully manage daily living tasks. An enriched lifestyle leads to increased cognitive activity and consequently improved cognition, including higher cognitive flexibility, which in turn may act as a protective mechanism against age-related memory decline. High neuroticism, on the other hand, leads to higher levels of stress and anxiety, which consequently may impair memory function (Airaksinen, Larsson, & Forsell, 2005; Lupien et al., 1997). There is also evidence that anticipation of stress, indicative for neuroticism, is linked to greater declarative memory impairments in older adults (Lupien et al., 1997).

From a neurobiological perspective, the hippocampus is greatly susceptible to the effects of stress (Kim, Pellman, & Kim, 2015). Stress is inversely related to hippocampal volume, indicating that low levels of stress can enhance memory performance, while severe and chronic stress can have deleterious effects (Wolf, 2003). The hippocampus regulates the production and release of the stress hormone cortisol (a glucocorticoid) via a neuroendocrine system, called the hypothalamic-pituitary-adrenal (HPA) axis (Frodl & O'Keane, 2013; Liu et al., 2017). The release of glucocorticoids leads to the production of glucose and the suppression of the immune system, enabling a fight-or-flight response in situations of perceived stress or danger. Glucocorticoid receptors can be found in large numbers in the hippocampus, which is also central to providing inhibitory feedback to the HPA axis (Frodl & O'Keane, 2013; Wolf, 2003). Excessive exposure to glucocorticoids can cause damage to the hippocampus, which in turn can impair inhibitory feedback and downregulation of the HPA axis and additional glucocorticoid release (Frodl & O'Keane, 2013). In particular, reduced hippocampal synaptic plasticity and neurogenesis can result from exposure to chronic or acute stress (Kim, Song, Kim, Song, & Kosten, 2006). Chronic stress due to high neuroticism and low levels of control beliefs as well as PTSD can

therefore cause structural and functional changes in the hippocampus, and ultimately lead to a dysregulation of the HPA axis and impaired memory function (Kim & Diamond, 2002). These associations are in line with our findings that personality traits that lead to higher levels of stress and anxiety are linked to memory impairments.

The findings described in Chapter 3, in particular regarding the role of stress and anxiety on memory function, led us to our next research question. We explored whether PTSD symptoms and/or early life stress (ELS) changes the shape (vertex-based) of the hippocampus and the amygdala, and impairs memory function (Chapter 4). We asked 70 combat veterans, who were exposed to trauma during their military deployment, to participate in a Magnetic Resonance Imaging (MRI) scan, neuropsychological assessment, a clinical interview, and to complete self-report measures. Hippocampus-dependent tests of episodic memory function were selected. During the clinical interview, we assessed whether the veterans met criteria for a diagnosis of PTSD (index trauma had to be deployment-related). Questionnaires captured symptom severity and exposure to ELS (domestic violence, sexual, physical, or emotional abuse) during childhood and/or adolescence. We found positive correlations between PTSD symptom severity and right hippocampal vertices as well as number of different types of ELS and vertices in the right hippocampus and right amygdala. These results indicate an association between PTSD symptoms and an expansion in hippocampal shape, and an association between ELS and an expansion in both hippocampal and amygdala shape. Overall volume of these brain regions was not affected by PTSD or ELS. Moreover, there were no associations between shape abnormalities, PTSD/ELS, and memory function. We did, however, find that more severe PTSD symptoms were linked to deficits in memory encoding but not to retention.

As these findings were in line with some, but not all previous studies, there are a number of considerations worth addressing. Deficits in declarative memory function have been reliably reported in PTSD (Gilbertson, Gurvits, Lasko, Orr, & Pitman, 2001; Samuelson et al., 2006; Wild & Gur, 2008) and ELS (De Bellis, Hooper, Spratt, & Woolley, 2009; Hedges & Woon, 2011). Although our results confirm correlations between severity of PTSD symptoms and memory impairments, we did not find that these associations were linked to structural brain abnormalities. Neither did we find that number of ELS affected memory performance. Since only a proportion of the sample participated in memory assessments, it is possible that our study was too underpowered to detect such associations.

Expansion of the amygdala can likely be explained by the involvement of this brain region in processing of emotions and stress. For example, functional MRI studies found increased amygdala activation in response to emotional faces (Dannlowski et al., 2012; van Harmelen et al., 2012) as well as increased connectivity between the amygdala and the hippocampus in individuals who have experienced childhood maltreatment (Jedd et al., 2015). Evidence from animal studies showing neuronal growth in the amygdala following severe stress (Cui, Sakamoto, Higashi, & Kawata, 2008; Popoli, Yan, McEwen, & Sanacora, 2012) and human studies linking increased amygdala volume to childhood

adversity (S. J. Lupien et al., 2011; Mehta et al., 2009) further support our findings of shape expansion in these limbic regions in veterans with ELS.

It is plausible, albeit speculative, that similar to the amygdala, expansion in hippocampal shape reflects excessive hippocampal activation in PTSD. Support for this theory comes from volumetric studies reporting larger hippocampi in taxi drivers (Maguire et al., 2000), individuals who meditate regularly (Kurth, Luders, Wu, & Black, 2014), as well as in individuals who study extensively (Koch, Reess, Rus, & Zimmer, 2016). These findings clearly show that certain activities can lead to increased hippocampal volume. PTSD has been linked to increased hippocampal activation during learning and recall of negative words (Brohawn, Offringa, Pfaff, Hughes, & Shin, 2010). Furthermore, PTSD is characterized by a tendency to search the environment for potential threat or harm, a behavior that may lead to overactive interactions between the amygdala and the hippocampus.

The number of PTSD studies measuring vertex-based shape as opposed to voxel-based volume in the hippocampus and the amygdala is quite limited (Akiki et al., 2017). The advantage of shape-based analyses is that these provide information about both indentation and expansion within the same structure. One recent study measuring shape abnormalities in the amygdala and the hippocampus reported opposite directionality than ours (Akiki et al., 2017). Akiki et al. (2017) point out that different subregions of the amygdala are associated with different behaviors (e.g., anxiety vs. emotion modulation), which may explain discrepancies between study findings. Moreover, it is possible that opposite directionalities, i.e., indentation and expansion, which are captured by shape analysis, are nullified during volume calculations. Nonetheless, there is clearly a need for more research into shape abnormalities in brain regions linked to memory function in individuals with PTSD and ELS.

PTSD often co-occurs with alcohol use disorder, and a diagnosis of both disorders is linked to more psychiatric and social problems (Driessen et al., 1998) as well as worse treatment outcomes (Najavits, Norman, Kivlahan, & Kosten, 2010) than either disorder alone. Structural changes in the hippocampus have been found in both PTSD (Felmingham et al., 2009; O'Doherty et al., 2017) and alcohol use disorder (Chanraud et al., 2009; Mechtcheriakov et al., 2007), which raises the question whether a dual diagnosis is associated with greater pathology in this brain region. Voxel-based morphometry (VBM) is a technique that measures concentration of gray matter as opposed to shape of brain structures (Ashburner & Friston, 2000). In **chapter 5**, we described a meta-analysis of VBM studies to assess gray matter volume loss in subjects with PTSD and subjects with alcohol use disorder compared to healthy controls. We subsequently examined the results for spatial overlap of gray matter volume loss across both disorders, and found shared gray matter deficits in bilateral dorsal and rostral anterior cingulate cortices (ACC) but not in the hippocampus. Neither did we find significant gray matter reductions in the hippocampus in either group alone.

These findings, although somewhat unexpected with regards to the hippocampus, suggest that abnormalities in the ACC present vulnerability for or consequence of

co-morbid PTSD and alcohol use disorder. The subdivisions of the ACC are involved in distinct functions via their neural connections with different brain regions. The dorsal ACC is mainly involved in cognitive tasks (e.g., error detection, decision making, conflict monitoring) (Botvinick & Braver, 2015; Bush et al., 2002), while the rostral-ventral ACC plays a crucial role in emotion regulation via connectivity with limbic structures (Etkin, Egner, & Kalisch, 2011; Mohanty et al., 2007). In PTSD, abnormal function of the ACC likely leads to a failure to inhibit attention to potential threats as well as an inability to down-regulate emotional responses to trauma-related stimuli (O'Doherty, Chitty, Saddiqui, Bennett, & Lagopoulos, 2015; Rauch, Shin, & Phelps, 2006). With regards to alcohol use disorder, impaired cognitive control via top-down regulation likely leads to continued drinking despite adverse consequences (Wilcox, Dekonenko, Mayer, Bogenschutz, & Turner, 2014). Although our meta-analysis did not show structural changes in the hippocampus, it is possible that a dysfunction in the ACC and its interaction with the hippocampus may underlie the symptomology observed in these disorders.

Chapter 6 of this dissertation discusses a unique case study of a young man (patient A.V.), who became severely amnesic following Herpes Simplex Encephalitis. The Herpes Simplex Encephalitis virus selectively targets and destroys neurons in the hippocampus and adjacent tissue in the medial temporal lobe (MTL) while sparing other brain regions (Damasio & Van Hoesen, 1985), leading to death if not treated immediately (Hierons, Janota, & Corsellis, 1978; Shaw & Alvord, 1997). A possible explanation for this disease pattern is the point of entry and route of the virus: the olfactory pathways and trigeminal nerves (Damasio & Van Hoesen, 1985). Alternatively, particular neuroanatomical and neurochemical properties of the MTL may allow the Herpes Simplex Encephalitis virus to attack this specific region (Damasio & Van Hoesen, 1985). Antiviral treatment with acyclovir, however, successfully stops the spread of the virus, and consequently, damage to the brain if administered in a timely manner. Brain lesions caused by Herpes Simplex Encephalitis provide an exceptionally effective opportunity to examine brain-behavior interactions with respect to the hippocampus and memory function. In order to characterize the structural and functional outcome of the Herpes Simplex Encephalitis infection in A.V., we conducted thorough neuropsychological assessments and analyses of MRI scans. These studies showed that the virus severely damaged A.V.'s MTL bilaterally, including the hippocampal formation, parahippocampal gyrus, entorhinal and perirhinal cortex, medial temporopolar cortex, and the amygdala. As a result, A.V. has profound anterograde amnesia, leaving him unable to learn new verbal and nonverbal information, while his other cognitive functions remained intact.

What makes the case of patient A.V. particularly valuable for neuroscientific research is not only his severe, yet selective, brain damage, but also his remarkable adaptation to this condition. With support from his mother, patient A.V. manages to live and function independently. He is able to compensate for his amnesia, largely through the use of his smartphone, which he utilizes to set reminders, take pictures, record facts, and navigate. Although these are functions of smart technology that most people use nowadays, for

A.V. this technology appears to take over functions of the MTL that would otherwise be absent. His intact procedural memory function likely allows him to learn how to utilize new technology and applications, while his high level of executive functioning facilitates a seamless and efficient use of new technologies.

METHODOLOGICAL CONSIDERATIONS

Several strengths and limitations need to be taken into consideration when interpreting the present work. The studies investigating the effect of lifestyle factors and personality traits on age-related memory decline are largely based on self-report measures, which may be influenced by response biases. This limitation could be addressed by using objective measures. In addition, with regards to alcohol consumption, we assessed alcoholic drinks consumed per week, which grouped occasional binge drinkers and regular light drinkers in the same category. It would be more useful to also collect data on maximum number of drinks consumed per day (i.e., binge drinking) and to assess for alcohol use disorder. Furthermore, the personality traits studied in this work did not include those of the big five personality dimensions as this model was not yet commonly used in research at the time LASA data collection started in 1992 (Zillig, Hemenover, & Dienstbier, 2002). Instead, our research focused on personality traits closely related to personal control beliefs as well as anxiety and stress.

Results from our cognitive aging studies need to be interpreted with caution as direct causal relationships between lifestyle and personality factors and memory function cannot be established. The potential role of mediators should be taken into consideration when interpreting associations between variables. For instance, individuals with higher levels of neuroticism may experience anxiety during neuropsychological assessments, which in turn could affect their performance. In addition, in some individuals a lowered sense of personal control may be the consequence of declining physical or cognitive health rather than reflect a stable personality construct. Likewise, it is not clear whether less social engagement and physical activity, and poor sleep quality are a consequence of declining cognition or vice versa. It is also important to note that the present study explored lifestyle factors and personality traits in late adulthood and did not assess these variables during early life. It is therefore not clear whether the observed associations are based on long-term effects, or whether engaging in certain behaviors and thought patterns later in life has the potential to improve or impair memory function.

Similarly, results from the present PTSD studies need to be interpreted carefully with regards to causality as additional factors should be taken into consideration. For instance, including different trauma types (i.e., trauma due to physical or sexual abuse or assault, combat, vehicle accidents, etc.) within the same cohort as well as time since trauma and age at trauma exposure, repeated trauma, time since symptom onset, comorbid psychiatric disorders, and sex are variables that may influence the relation between PTSD, morphological abnormalities, and memory performance. It is important to highlight that

reduced ACC volumes have been found in a number of mental health disorders (Goodkind et al., 2015), and may therefore not be specific to co-morbid PTSD and alcohol use disorder but rather reflect a neural substrate shared with several psychopathologies. Furthermore, the present studies do not answer the question whether gray matter reductions in the ACC represent a precursor to or a consequence of PTSD and alcohol use disorder, or whether shape expansion in the hippocampus and the amygdala are a precursor to or a consequence of PTSD/ELS. Causality may be better addressed by prospective, longitudinal studies. Differences in the selection of control subjects also need to be taken into consideration as PTSD studies commonly do not account for trauma exposure in the control cohort. Similarly, while PTSD studies often exclude alcohol use disorder, alcohol use disorder studies typically do not account for trauma exposure in their study sample. For that reason, we excluded PTSD studies with trauma-exposed control cohorts from the meta-analysis. Another area of concern is that both occasional alcohol use and alcohol abstinence are both frequently used as control cohorts in alcohol use disorder studies. These methodological considerations were not controlled for in the meta-analysis.

There are a number of strengths of the present research that are important to point out. For example, the LASA-based studies include a large-community based cohort and prospective longitudinal research design. Analyses with large sample sizes increase statistical power. Our research therefore provides valuable data by assessing cognitive decline within the same subject over a period of 14 years. It is possible that attrition produced a potential bias, as patients with certain personality traits or lifestyle habits may have been more likely to have dropped out of the study. The statistical method used in the analyses (i.e., linear mixed models), however, does not exclude dropped-out subjects in the longitudinal analyses, therefore reducing such bias. An additional strength of all of our studies is that subjects participated in comprehensive neuropsychological assessments as opposed to using short cognitive screening tests. Across all studies, we used well-validated memory tests and assessed immediate as well as delayed recall and recognition of word lists. The PTSD studies also included assessments of both verbal and visual memory function. An additional strength of the present work is that potential variability in the PTSD study was reduced by including a homogeneous subject cohort (i.e., male post 9/11 combat veterans with deployment-related trauma).

CLINICAL IMPLICATIONS AND SUGGESTIONS FOR FUTURE RESEARCH

The present research offers compelling findings with regards to the effects of modifiable lifestyle factors on cognitive health and provides important clinical implications. Our findings may help identify older adults who are at a greater risk for memory deficits and promote lifestyle choices that are beneficial for cognitive health. In essence, our work provides support for two categories of protective lifestyle factors to delay age-related cognitive decline: cardiovascular health and social engagement. Cardiovascular health

can be promoted by physical activity and mild-to-moderate alcohol consumption as well as abstaining from smoking tobacco. These lifestyle habits are linked to reduced risks of stroke and congestive heart failure, and reduced inflammation, which is at a neural level associated with increased neurogenesis, synaptic plasticity, and gray matter volume in the hippocampus. An enriched lifestyle, on the other hand, characterized by incorporating socially and mentally stimulating activities in everyday life, promotes increased cognitive activity which can in turn improve cognitive function. In addition, engaging in social activities and maintaining relationships likely provides a sense of purpose and motivates self-care and independence.

Our findings provide support for two different clinical approaches regarding the effects of personality traits on memory function. First, our findings are in line with other studies that have found that training aimed at improving cognitive functioning in older adults improves individuals' perceived sense of control (Wolinsky et al., 2009). Second, training that increases self-efficacy (West, Bagwell, & Dark-Freudeman, 2008) as well as meditation techniques that reduce anxiety (Zeidan, Johnson, Diamond, David, & Goolkasian, 2010) have been found to improve cognitive function. The present findings therefore stress the need to develop and validate intervention programs for older adults aimed at both improving perceived self-control and lowering stress and anxiety. Moreover, offering such trainings to older adults who may be at an increased risk for cognitive decline may be beneficial in improving the quality of life in this population.

For future research, it would be interesting to study the neural correlates of the associations between lifestyle factors and personality traits on memory function in older adults. For instance, our findings raise the question whether the effects of lifestyle factors and personality traits on age-related decline are linked to differences in gray matter or white matter changes in certain brain regions like the hippocampus. Investigating the interactions between different lifestyle factors may also provide valuable insight. For example, what is the impact of physical activity and alcohol consumption on sleep quality, and how does this interaction in turn affect memory function?

We also have some suggestions regarding future PTSD research. Previous trauma exposure is commonly seen in those with heavy drinking (Schwandt, Heilig, Hommer, George, & Ramchandani, 2013; Stewart, 1996) and trauma exposure itself is linked to structural brain changes (O'Doherty et al., 2015). It is therefore crucial that both PTSD and alcohol use disorder studies assess exposure to traumatic experiences or ELS that might have occurred prior to and in addition to the trauma linked to the onset of PTSD. On the other hand, it would be extremely valuable if PTSD studies would track alcohol consumption. Investigating the functional interactions between the hippocampus and the ACC may provide valuable insights into the symptomatology of co-morbid PTSD and alcohol use disorder.

And lastly, we presented the thorough examination of a patient with bilateral damage to the MTL following a life-threatening bout of Herpes Simplex Encephalitis. While we provided a detailed account of the clinical picture associated with the complete loss

of hippocampal function, numerous questions remain unanswered. Considering A.V.'s extensive damage to limbic regions, including the amygdala and the insula, it is important for future investigations to examine his psychiatric and emotional functions. In addition, it would be interesting to investigate A.V.'s navigation skills and spatial memory. Although he largely relies on his smart phone for driving, he also does not show difficulties finding his way without assistance if the routes are familiar to him.

The case of patient A.V. illustrates the significant role that smart technology can play in the management of memory disorders due to aging, dementia, PTSD, stroke, tumors, hypoxia, or traumatic brain injury. Smart devices and digital tools with functions such as calendars, reminders, alerts, cameras, contact lists, and navigation enable patients with amnesia or severe memory impairments to function in the 21st century. These recent technological developments have sparked research in the field of rehabilitation to explore how these devices can be utilized to assist patients with memory deficits. On the one hand, new technologies can play an important role in assisting people with cognitive impairment and enabling them to live independently. On the other hand, frequent use and reliance on smart technology may prevent early detection of declining memory function and consequently delay medical treatment.

REFERENCES

Aase, D. M., DiGangi, J. A., Babione, J. M., Schroth, C., Levy, D. M., Kennedy, A. E.,…Passi, H. (2017). PTSD symptoms are associated with visual retrieval performance in OEF/OIF/OND veterans. *Psychiatry research, 257*, 156-162.

Airaksinen, E., Larsson, M., & Forsell, Y. (2005). Neuropsychological functions in anxiety disorders in population-based samples: evidence of episodic memory dysfunction. *Journal of psychiatric research, 39*(2), 207-214.

Akiki, T. J., Averill, C. L., Wrocklage, K. M., Schweinsburg, B., Scott, J. C., Martini, B.,… Abdallah, C. G. (2017). The association of PTSD symptom severity with localized hippocampus and amygdala abnormalities. *Chronic Stress, 1*, 2470547017724069.

Ashburner, J., & Friston, K. J. (2000). Voxel-based morphometry—the methods. *NeuroImage, 11*(6), 805-821.

Bandura, A. (1989). Regulation of cognitive processes through perceived self-efficacy. *Developmental Psychology, 25*(5), 729.

Bartsch, T., & Wulff, P. (2015). The hippocampus in aging and disease: from plasticity to vulnerability: Elsevier.

Bennett, D. A., Schneider, J. A., Tang, Y., Arnold, S. E., & Wilson, R. S. (2006). The effect of social networks on the relation between Alzheimer's disease pathology and level of cognitive function in old people: a longitudinal cohort study. *The Lancet Neurology, 5*(5), 406-412.

Bettio, L. E., Rajendran, L., & Gil-Mohapel, J. (2017). The effects of aging in the hippocampus and cognitive decline. *Neuroscience & Biobehavioral Reviews, 79*, 66-86.

Boldrini, M., Underwood, M. D., Hen, R., Rosoklija, G. B., Dwork, A. J., Mann, J. J., & Arango, V. (2009). Antidepressants increase neural progenitor cells in the human hippocampus. *Neuropsychopharmacology, 34*(11), 2376.

Botvinick, M., & Braver, T. (2015). Motivation and cognitive control: from behavior to neural mechanism. *Annual review of psychology, 66*, 83-113.

Broadbent, N. J., Squire, L. R., & Clark, R. E. (2004). Spatial memory, recognition memory, and the hippocampus. *Proceedings of the National Academy of Sciences, 101*(40), 14515-14520.

Brohawn, K. H., Offringa, R., Pfaff, D. L., Hughes, K. C., & Shin, L. M. (2010). The neural correlates of emotional memory in posttraumatic stress disorder. *Biological Psychiatry, 68*(11), 1023-1030.

Bruno, R. S., & Traber, M. G. (2006). Vitamin E biokinetics, oxidative stress and cigarette smoking. *Pathophysiology, 13*(3), 143-149.

Bush, G., Vogt, B. A., Holmes, J., Dale, A. M., Greve, D., Jenike, M. A., & Rosen, B. R. (2002). Dorsal anterior cingulate cortex: a role in reward-based decision making. *Proceedings of the National Academy of Sciences, 99*(1), 523-528.

Cabeza, R., & St Jacques, P. (2007). Functional neuroimaging of autobiographical memory. *Trends in cognitive sciences, 11*(5), 219-227.

Cacioppo, J. T., & Hawkley, L. C. (2009). Perceived social isolation and cognition. *Trends in cognitive sciences, 13*(10), 447-454.

Chanraud, S., Leroy, C., Martelli, C., Kostogianni, N., Delain, F., Aubin, H.-J., … Martinot, J.-L. (2009). Episodic memory in detoxified alcoholics: contribution of grey matter microstructure alteration. *PLoS One, 4*(8), e6786.

Cotman, C. W., Berchtold, N. C., & Christie, L.-A. (2007). Exercise builds brain health: key roles of growth factor cascades and inflammation. *Trends in neurosciences, 30*(9), 464-472.

Cramer, S. C., Sur, M., Dobkin, B. H., O'brien, C., Sanger, T. D., Trojanowski, J. Q.,…Chen, D. (2011). Harnessing neuroplasticity for clinical applications. *Brain, 134*(6), 1591-1609.

Cui, H., Sakamoto, H., Higashi, S., & Kawata, M. (2008). Effects of single-prolonged stress on neurons and their afferent inputs in the amygdala. *Neuroscience, 152*(3), 703-712.

Damasio, A., & Van Hoesen, G. (1985). The limbic system and the localisation of herpes simplex encephalitis. *Journal of Neurology, Neurosurgery & Psychiatry, 48*(4), 297-301.

Dannlowski, U., Stuhrmann, A., Beutelmann, V., Zwanzger, P., Lenzen, T., Grotegerd, D.,..Bauer, J. (2012). Limbic scars: long-term consequences of childhood maltreatment revealed by functional and structural magnetic resonance imaging. *Biological psychiatry, 71*(4), 286-293.

Driessen, M., Veltrup, C., Weber, J., John, U., Wetterling, T., & Dilling, H. (1998). Psychiatric co-morbidity, suicidal behaviour and suicidal ideation in alcoholics seeking treatment. *Addiction, 93*(6), 889-894.

Eichenbaum, H. (2001). The hippocampus and declarative memory: cognitive mechanisms and neural codes. *Behavioural brain research, 127*(1-2), 199-207.

Erickson, K. I., Hillman, C. H., & Kramer, A. F. (2015). Physical activity, brain, and cognition. *Current opinion in behavioral sciences, 4*, 27-32.

Etkin, A., Egner, T., & Kalisch, R. (2011). Emotional processing in anterior cingulate and medial prefrontal cortex. *Trends in cognitive sciences, 15*(2), 85-93.

Fanselow, M. S., & Dong, H.-W. (2010). Are the dorsal and ventral hippocampus functionally distinct structures? *Neuron, 65*(1), 7-19.

Felmingham, K., Williams, L. M., Whitford, T. J., Falconer, E., Kemp, A. H., Peduto, A., & Bryant, R. A. (2009). Duration of posttraumatic stress disorder predicts hippocampal grey matter loss. *Neuroreport, 20*(16), 1402-1406.

Frodl, T., & O'Keane, V. (2013). How does the brain deal with cumulative stress? A review with focus on developmental stress, HPA axis function and hippocampal structure in humans. *Neurobiology of disease, 52*, 24-37.

Gilbertson, M. W., Gurvits, T. V., Lasko, N. B., Orr, S. P., & Pitman, R. K. (2001). Multivariate assessment of explicit memory function in combat veterans with posttraumatic stress disorder. *Journal of Traumatic Stress, 14*(2), 413-432.

Goodkind, M., Eickhoff, S. B., Oathes, D. J., Jiang, Y., Chang, A., Jones-Hagata, L. B.,.. Korgaonkar, M. S. (2015). Identification of a common neurobiological substrate for mental illness. *JAMA psychiatry, 72*(4), 305-315.

Hierons, R., Janota, I., & Corsellis, J. (1978). The late effects of necrotizing encephalitis of the temporal lobes and limbic areas: a clinico-pathological study of 10 cases. *Psychological Medicine, 8*(1), 21-42.

Jedd, K., Hunt, R. H., Cicchetti, D., Hunt, E., Cowell, R. A., Rogosch, F. A.,…Thomas, K. M. (2015). Long-term consequences of childhood maltreatment: Altered amygdala functional connectivity. *Development and psychopathology, 27*(4pt2), 1577-1589.

Johnsen, G. E., & Asbjørnsen, A. E. (2008). Consistent impaired verbal memory in PTSD: a meta-analysis. *Journal of Affective Disorders, 111*(1), 74-82.

Kempermann, G., Gage, F. H., Aigner, L., Song, H., Curtis, M. A., Thuret, S.,…Cameron, H. A. (2018). Human adult neurogenesis: evidence and remaining questions. *Cell Stem Cell*.

Kim, E. J., Pellman, B., & Kim, J. J. (2015). Stress effects on the hippocampus: a critical review. *Learning & memory, 22*(9), 411-416.

Kim, J. J., & Diamond, D. M. (2002). The stressed hippocampus, synaptic plasticity and lost memories. *Nature Reviews Neuroscience, 3*(6), 453.

Kim, J. J., Song, E. Y., Kim, J. J., Song, E. Y., & Kosten, T. A. (2006). Stress effects in the hippocampus: synaptic plasticity and memory. *Stress, 9*(1), 1-11.

Koch, K., Reess, T. J., Rus, O. G., & Zimmer, C. (2016). Extensive learning is associated with gray matter changes in the right hippocampus. *NeuroImage, 125*, 627-632.

Krueger, K. R., Wilson, R. S., Kamenetsky, J. M., Barnes, L. L., Bienias, J. L., & Bennett, D. A. (2009). Social engagement and cognitive function in old age. *Experimental aging research, 35*(1), 45-60.

Kurth, F., Luders, E., Wu, B., & Black, D. S. (2014). Brain gray matter changes associated with mindfulness meditation in older adults: an exploratory pilot study using voxel-based morphometry. *Neuro: Open Journal, 1*(1), 23-26.

Lie, D. C., Song, H., Colamarino, S. A., Ming, G.-l., & Gage, F. H. (2004). Neurogenesis in the adult brain: new strategies for central nervous system diseases. *Annual Review of Pharmacology and Toxicology, 44*, 399-421.

Liu, W., Ge, T., Leng, Y., Pan, Z., Fan, J., Yang, W., & Cui, R. (2017). The role of neural plasticity in depression: from hippocampus to prefrontal cortex. *Neural Plasticity, 2017*, 1-11.

Lupien, S., Gaudreau, S., Tchiteya, B., Maheu, F., Sharma, S., Nair, N.,…Meaney, M. (1997). Stress-induced declarative memory impairment in healthy elderly subjects: relationship to cortisol reactivity. *The Journal of Clinical Endocrinology & Metabolism, 82*(7), 2070-2075.

Lupien, S. J., Parent, S., Evans, A. C., Tremblay, R. E., Zelazo, P. D., Corbo, V.,…Séguin, J. R. (2011). Larger amygdala but no change in hippocampal volume in 10-year-old children exposed to maternal depressive symptomatology since birth. *Proceedings of the National Academy of Sciences, 108*(34), 14324-14329.

Maguire, E. A., Gadian, D. G., Johnsrude, I. S., Good, C. D., Ashburner, J., Frackowiak, R. S., & Frith, C. D. (2000). Navigation-related structural change in the hippocampi of taxi drivers. *Proceedings of the National Academy of Sciences, 97*(8), 4398-4403.

Mayo, L. M., & Heilig, M. (2018). A Hippocampal Signature of Posttraumatic Stress Disorder Vulnerability. *Biological Psychiatry, 84*(2), 78-79.

Mechtcheriakov, S., Brenneis, C., Egger, K., Koppelstaetter, F., Schocke, M., & Marksteiner, J. (2007). A widespread distinct pattern of cerebral atrophy in patients with alcohol addiction revealed by voxel-based morphometry. *Journal of Neurology, Neurosurgery & Psychiatry, 78*(6), 610-614.

Mehta, M. A., Golembo, N. I., Nosarti, C., Colvert, E., Mota, A., Williams, S. C.,…Sonuga-Barke, E. J. (2009). Amygdala, hippocampal and corpus callosum size following severe early institutional deprivation: the English and Romanian Adoptees study pilot. *Journal of Child Psychology and Psychiatry, 50*(8), 943-951.

Meyer, J. S., Rauch, G. M., Crawford, K., Rauch, R. A., Konno, S., Akiyama, H.,…Haque, A. (1999). Risk factors accelerating cerebral degenerative changes, cognitive decline and dementia. *International Journal of Geriatric Psychiatry, 14*(12), 1050-1061.

Mohanty, A., Engels, A. S., Herrington, J. D., Heller, W., Ringo Ho, M. H., Banich, M. T.,.. Miller, G. A. (2007). Differential engagement of anterior cingulate cortex subdivisions for cognitive and emotional function. *Psychophysiology, 44*(3), 343-351.

Najavits, L. M., Norman, S. B., Kivlahan, D., & Kosten, T. R. (2010). Improving PTSD/ substance abuse treatment in the VA: A survey of providers. *The American Journal on Addictions, 19*(3), 257-263.

O'Doherty, D. C., Chitty, K. M., Saddiqui, S., Bennett, M. R., & Lagopoulos, J. (2015). A systematic review and meta-analysis of magnetic resonance imaging measurement of structural volumes in posttraumatic stress disorder. *Psychiatry Research: Neuroimaging, 232*(1), 1-33.

O'Doherty, D. C., Tickell, A., Ryder, W., Chan, C., Hermens, D. F., Bennett, M. R., & Lagopoulos, J. (2017). Frontal and subcortical grey matter reductions in PTSD. *Psychiatry Research: Neuroimaging, 266*, 1-9.

O'Keefe, J. H., Bhatti, S. K., Bajwa, A., DiNicolantonio, J. J., & Lavie, C. J. (2014). *Alcohol and cardiovascular health: the dose makes the poison… or the remedy.* Paper presented at the Mayo Clinic Proceedings.

Popoli, M., Yan, Z., McEwen, B. S., & Sanacora, G. (2012). The stressed synapse: the impact of stress and glucocorticoids on glutamate transmission. *Nature Reviews Neuroscience, 13*(1), 22.

Rauch, S. L., Shin, L. M., & Phelps, E. A. (2006). Neurocircuitry models of posttraumatic stress disorder and extinction: human neuroimaging research—past, present, and future. *Biological Psychiatry, 60*(4), 376-382.

Samuelson, K. W., Neylan, T. C., Metzler, T. J., Lenoci, M., Rothlind, J., Henn-Haase, C.,… Marmar, C. R. (2006). Neuropsychological functioning in posttraumatic stress disorder and alcohol abuse. *Neuropsychology, 20*(6), 716.

Schwandt, M. L., Heilig, M., Hommer, D. W., George, D. T., & Ramchandani, V. A. (2013). Childhood trauma exposure and alcohol dependence severity in adulthood: mediation by emotional abuse severity and neuroticism. *Alcoholism: Clinical and Experimental Research, 37*(6), 984-992.

Seeman, T., McAvay, G., Merrill, S., Albert, M., & Rodin, J. (1996). Self-efficacy beliefs and change in cognitive performance: MacArthur studies on Successful Aging. *Psychology and Aging, 11*(3), 538-551.

Shaw, C.-M., & Alvord, J. E. (1997). Neuropathology of the limbic system. *Neuroimaging Clinics of North America, 7*(1), 101-142.

Stewart, S. H. (1996). Alcohol abuse in individuals exposed to trauma: a critical review. *Psychological bulletin, 120*(1), 83-112.

van Harmelen, A.-L., van Tol, M.-J., Demenescu, L. R., van der Wee, N. J., Veltman, D. J., Aleman, A.,…Elzinga, B. M. (2012). Enhanced amygdala reactivity to emotional faces in adults reporting childhood emotional maltreatment. *Social Cognitive and Affective Neuroscience, 8*(4), 362-369.

Vermetten, E., Vythilingam, M., Southwick, S. M., Charney, D. S., & Bremner, J. D. (2003). Long-term treatment with paroxetine increases verbal declarative memory and hippocampal volume in posttraumatic stress disorder. *Biological Psychiatry, 54*(7), 693-702.

West, R. L., Bagwell, D. K., & Dark-Freudeman, A. (2008). Self-efficacy and memory aging: The impact of a memory intervention based on self-efficacy. *Aging, Neuropsychology, and Cognition, 15*(3), 302-329.

Wilcox, C. E., Dekonenko, C. J., Mayer, A. R., Bogenschutz, M. P., & Turner, J. A. (2014). Cognitive control in alcohol use disorder: deficits and clinical relevance. *Reviews in the Neurosciences, 25*(1), 1-24.

Wild, J., & Gur, R. C. (2008). Verbal memory and treatment response in post-traumatic stress disorder. *The British Journal of Psychiatry, 193*(3), 254-255.

Wolf, O. (2003). HPA axis and memory. *Best Practice & Research Clinical Endocrinology & Metabolism, 17*(2), 287-299.

Wolinsky, F. D., Vander Weg, M. W., Martin, R., Unverzagt, F. W., Willis, S. L., Marsiske, M.,…Tennstedt, S. L. (2009). Does cognitive training improve internal locus of control among older adults? *Journals of Gerontology Series B: Psychological Sciences and Social Sciences, 65*(5), 591-598.

Zeidan, F., Johnson, S. K., Diamond, B. J., David, Z., & Goolkasian, P. (2010). Mindfulness meditation improves cognition: Evidence of brief mental training. *Consciousness and cognition, 19*(2), 597-605.

Zillig, L. M. P., Hemenover, S. H., & Dienstbier, R. A. (2002). What do we assess when we assess a Big 5 trait? A content analysis of the affective, behavioral, and cognitive processes represented in Big 5 personality inventories. *Personality and Social Psychology Bulletin, 28*(6), 847-858.

Zola-Morgan, S., & Squire, L. R. (1993). Neuroanatomy of memory. *Annual Review of Neuroscience, 16*(1), 547-563.